Transcript of Hallek Interview Part 2

Marti: With regards to the Binet A patients, what kind of symptoms was required of them in order to be treated?

Hallek: Yeah, so usually we don't include patients with Binet stage A. And in this trial, they had to be—they had to present with severe symptoms like night sweats, weight loss, and then they could be included in the trial. And it's only a very small group of patients.

Marti: I've often read, and I think I've heard it said, perhaps one of the uses of prognostic factors is that 50% of stage A Binet patients progress during the 2, 3-year period of observation. Would you concur with that?

Hallek: Yes. So, it's about half of them. We actually, maybe it's—have the following distinction Guillaume Dighiero used to make it, and I usually, I comply with this. It's about a third of our patients that never requires any treatment, and we should protect them from that because they are stable over a very long time. Then, there's about another third that develops within the first, let's say, 3-4 years, and those are the population that is to be studied, whether earlier treatment is giving benefit to them. And then, in the middle there is something many of the unmutated IGVH patients, by the way, that can develop over 8 years or 10 years into a disease that needs treatment and where we don't know what we should do in the beginning with. I would probably watch them right now.

So, our current trial strategy is exactly to identify this one third, currently it's between 20% and 30% of these high-risk patients in stage A, and we do randomized trials. So, we have done one that is beginning to mature. It takes a long time. That was bcl in one trial, the one that I actually started with in 1994. So, we will see whether fludarabine alone will have a benefit there. I don't think so.

Now, we have done FCR, early on. That's the CLL 7 protocol, exactly to answer this question whether early intervention in high-risk patients in CLL is giving any benefit. So, it is a FCR early treatment versus delayed treatment, and the study is actually finishing right now. We probably will close it in July or August.

Marti: And that's CLL 7?

Hallek: That's CLL 7 and it's exactly answering—trying to answer this question whether high-risk situations in early stage require treatment or benefit from early intervention.

Marti: Recently, and you alluded to this in your presentation this morning, although you didn't go into great detail, the revision of the, what, 1994, 1996?

Hallek: 1996 guidelines?[1] Yeah.

Marti: And revised twice. This is—yeah, this is the second revision.

Hallek: Yes, exactly.

Marti: And your comment was something to the effect that each paragraph was meticulously went over, which I think is good.

Hallek: Yes.

Marti: I know that you're aware of that the addition of MBL into these revised guidelines caused some controversy.

Hallek: Yes.

Marti: How—what was the name—how was that controversy perceived, say, in Germany or Europe?

Hallek: Well, actually we had a—this is a real story that is funny, because with the initial paragraph that we wrote there was not so carefully written as it should be, and we basically had said at that time that we would add the B lymphocytes and then would use the same criterion also for calling a complete remission a complete remission, which would have changed the definition of complete remission totally. And so that, we had a lot of debate about these criteria in terms of defining CRs, which we have resolved in a later revision, but for the MBL, it was not such a big deal in Europe. It was more here and in Australia. We got two comments about this basically saying that it would change the definition of the disease too much and it would therefore create totally different clinical trials in the future.

And I think that has by and large been overcome by the two recent publications in the *New England Journal*, particularly the one by Andy Rawstron who clearly showed that below a certain threshold of 5000 B lymphocytes, the risk of getting full-blown CLL was relatively low.[2] And that actually resolved the issue. So, I think now actually with work that you have contributed to and others, we see a relatively solid

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[1] Michael Hallek, Bruce D. Cheson, Daniel Catovsky, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. *Blood.* 2008;111(12):5446–5456.
[2] Rawstron AC, Bennett FL, O'Connor SJ, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. *N Engl J Med*. 2008;359(6):575-583.

acceptance of the concept of monoclonal B cell lymphocytosis, as opposed to a CLL that is, can be a very aggressive disease. And I think it's a very good thing to have happened.

And that is also the echo and the response that I get from European physicians, because all of us know that we have some of these people that we called leukemic in the past, with minimal lymphocyte counts, and they were frightened about the name, but not—had—basically did not suffer from the disease. So, the worst thing that they had was the name of the disease. And I think we moved that threshold with the guidelines and with the papers on MBL upwards to 5000 B lymphocytes, and I think it's a very, very good move. It's a very important contribution, I think, and I think the guidelines were right to actually include that into their definitions.

Marti: I think it—I think the controversy that it generated was excellent.

Hallek: Yes.

Marti: I mean I, I think it—

Hallek: Correct.

Marti: I know we're on—this is an editorial comment that perhaps I shouldn't make, but early on, we took great care to avoid changing the definition of CLL because we never felt that was our charge. In retrospect, maybe we should have hammered away at that more, but that's ok.

Hallek: Mmhmm.

Marti: Another question that—this is just somewhat of a personal interest—in our research protocol here, for the natural history, in patients that are having a rapid change in lymph nodes growth, and in a three compartment study looking at microarray expression in both the, simultaneously in the blood, marrow, and lymph node, we sometimes use PET scanning to help select a lymph node that might show greater uptake than usual. What about the role of MRI in scanning the bone marrow, looking for the degree of bone marrow involvement?

Hallek: So, that's a good idea, although we have no experience and data whatsoever on that. So, while I think MRI has an extremely high resolution, as we know from studies in multiple myeloma, all of us know that, to really look what's going on at the marrow. However, we have not evaluated this at all in any of our trials, and so I would say that this is one of the things that we might do, for maybe also the definition of MRD. When this is something that will occupy and preoccupy us over the coming years, to move towards long-term

remissions. I'm not even—I'm no longer using intentionally the word "cure," because it doesn't really matter, you know? For a patient who is without any symptoms for 20 or 30 years after a first treatment that's what "cure" is, for those patients at least.

So, if we wish to achieve those states in many patients with CLL and I think we can do that very soon, we are about to do that right now. Attempts to maintain the patients in an MRD-negative state are the right way to go, and we could eventually use MRD and assess the marrow, the overall picture of the marrow to see whether there's any spot where disease comes up again. A very good study question for the future, but I have no personal experience. Yeah.

Marti: And another question is the role of splenectomy in CLL. The medical and surgical management of massive splenomegaly. Would you care to comment upon that?

Hallek: Yeah, so, within the novel treatments it has become less frequent too, but I am still using it. So, some patients, when they come to a refractory situation or they have a large bulk or large spleen, suffer from that and you can't do much about it. I frequently proceed to splenectomy. It's maybe even underestimated right now. So, it is relieving symptoms and so very often you get recovery of cell counts quickly, and that's still something that we should not forget.

Marti: If, in terms of a protocol evaluation of the role of splenectomy in CLL, how would one go about that? And maybe in terms of a caveat, to start such a discussion, what is the natural history of splenomegaly in CLL?

Hallek: Hmm. That's again a good question. I start with the second because it's easier. A protocol on splenectomy is, I think, extremely difficult of any kind because it's too rare. I mean, from, I would guess in 100 patients or 200 a year I would do it once or so, and so it's a very rare therapeutic event. But simply should not be forgotten because sometimes it's a quickly acting therapeutic measure, and I have seen patients that were considered to be hopeless because nothing worked and then we did splenectomy and could start with a novel treatment again afterwards.

But then natural history…I mean, it's certainly a poor prognostic marker. It is eventually part of the 11q-minus patients that are having a different history but we can treat them well. So, see, that's why—maybe that has become more rare because the patients with large lymph nodes plus large spleens now with the combination therapies are improved a lot, but while with the older treatment regimens, we didn't do that. So maybe that's why we're seeing them more rarely.

I think—if I think about the spleen right now, I think more about it as the natural homing organ of CLL cells, and what we need to understand is the composition of this homing organ and to understand the composition of the microenvironment of the CLL. That seems to be different, as I learned here, in the marrow, the spleen, the liver, and the blood. So, there is different compartments that behave differently and the spleen is a highly interesting organ.

We have done studies in TCL1 mice, see proliferation zones that are highly full of macrophages, and it seems like the spleen is acting as a very strong promoter of disease development in these, in this situation. But how are we going to explore that clinically? I just don't know yet.

Marti: I like your allusion to the TCL1 mouse. We've spent a lot of time looking at the NZB, but one of the reasons for thinking about splenectomy in the CLL patient is almost more exclusively research, and that would be able to do microarray expression analysis.

Hallek: Yes.

Marti: And how would one justify getting splenic tissue in that setting, in the CLL setting? If—because I think oftentimes, in early disease, you—the patient doesn't have much lymphadenopathy and the splenomegaly predominates. I find a lot of patients that are referred here often come with a spleen that's undetected. And I'm not talking massive, 6 centimeters below, usually less than that.

Hallek: Yeah, that's—

Marti: I often wonder how would we justify, I guess a biopsy would have to be done under direct vision?

Hallek: Yeah, and—

Marti: Radiofrequency ablation?

Hallek: Yes, and that's actually something that would be—we need to develop this technology, I would say, because you have always a risk of massive bleeding in the spleen. Liver biopsies could be a better place to do that, if they are infiltrated, but the risk of bleeding that is, as you say, could be under—if possible at all—under good conditions where you have coagulation available immediately. And splenectomies, I would say patients that are cytopenic and resistant to other therapies could be a group where you could get them, but this would not allow you to go in the early phases of the disease where you look at the homing organ spleen, where I wouldn't do it.

I'm—I mean, that's one of the—and so, your question is also a little bit on the ethical and other concerns of one of the, I would call it, "golden rules," although I think that is not a judgment about our trials but what—it is a golden rule—we are, I'm always asking at the end of a trial design in our group of people in Cologne and then in the strategic commission, as we call it, of our study group, "Would we include our mother in our trial?" And so, everything that is done is done in a way that we say, "Yes, if I'm sick, I would include myself into this trial." And so, with this ethical comment, I would not see a person without any symptoms to be splenectomized or biopsied in the spleen because it has certain risks. It's only justified if you have cytopenias, I would say.

Marti: And in terms of, say, somebody who was unmutated and unfavorable cytogenetics, CD38-positive, ZAP-70-positive, β_2 microglobulin 3.5, the treat—I'm trying to envision a situation where a splenectomy might make management of a patient more favorable.

Hallek: Hmm. Needs to be proven, though. I mean, it would be a question of a randomized comparison, if you wanted that. I would say the patient information is not an easy one in this case.

Marti: Okay.

Hallek: If you ask a patient whether or not in a randomized way you would take out his spleen, he would probably, well, just leave you one option. [Laughs]

Marti: And if the biostatisticians said that you needed, say, five, and have five, what would the end point be? Obviously cytopenias shouldn't develop because of secondary hypersplenism, but—

Hallek: Yeah. That is—I, that's what I would choose. I mean, basically to start that, I would probably choose a population where you can clinically justify this, and it is—there's good papers out there to justify splenectomy as a good therapeutic measure. And then see, your end point is long-term control of cytopenias.

Marti: Yes.

Hallek: That, with a handful of patients can be—I think can be convincingly done. But the only disadvantage of that being that you won't access the group of early stage, no symptom patients, but that's probably fine.

Marti: Just as well. They'll never need it anyway.

Hallek: Yes.